Swiss Public Summary of the Risk Management Plan (RMP)

for

Trodelvy®180 mg, Powder for concentrate for solution for infusion

(Sacituzumab govitecan)

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SUMMARY OF RISK MANAGEMENT PLAN FOR TRODELVY® (SACITUZUMAB GOVITECAN)

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.

The RMP summary of TRODELVY is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the „Arzneimittelinformation / Information sur le médicament“ approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of TRODELVY in Switzerland is the „Arzneimittelinformation / Information sur le médicament“ (see www.swissmedic.ch) approved authorized by Swissmedic. Gilead Sciences Switzerland Sàrl is fully responsible for the accuracy and correctness of the content of the here published summary RMP of TRODELVY.

I. The Medicine and What is it Used for

TRODELVY is authorized as a monotherapy for the treatment of adult patients with unresectable or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, including at least one of them for advanced disease (see SmPC for the full indication). It contains sacituzumab govitecan as the active substance and it is given as an intravenous infusion. Further information about the evaluation of TRODELVY's benefits can be found in TRODELVY's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/trodelvy.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of TRODELVY, together with measures to minimise such risks and the proposed studies for learning more about TRODELVY's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of TRODELVY is not yet available, it is listed under 'missing information' below.

II.A. List of important risks and missing information

Important risks of TRODELVY are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of TRODELVY. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

Table Part VI.1. List of Important Risks and Missing Information

Important Identified Risks	Serious infections secondary to neutropenia
	Severe diarrhoea
	Hypersensitivity
Important Potential Risks	Embryo-foetal toxicity
Missing Information	Use in patients with moderate or severe hepatic impairment
	Immunogenicity

II.B. Summary of Important Risks

TRODELVY has been assigned legal status of a medicine subject to medical prescription in the European Union (EU), whereby therapy should only be prescribed and administered by a healthcare professional experiences in the use of anti-cancer therapies (as described in section 4.2 of the SmPC).

Table Part VI.2. Summary of Important Risks and Missing Information

Important Identified Risk	**Serious infections secondary to neutropenia**
Evidence for linking the risk to the medicine	In the clinical studies 65.6% of 366 patients treated with SG had neutropenia and in 51.6% patients the neutropenia was severe. The dose of SG was interrupted in

	42.6% patients and reduced in 7.7% patients. However, no patients had to discontinue SG permanently because of neutropenia. Infections potentially associated with neutropenia occurred in 11.2% of 366 patients and were severe in 4.1% of patients. Serious infections potentially associated with neutropenia occurred in 2.7% of 366 patients. In most cases (10.4%) the patients recovered from the infection. The dose of SG was interrupted in 1.9% patients, reduced in 0.3% patients and permanently discontinued in 0.5% of patients. Neutropenia was one of the main toxicities seen in animal studies. Clinical studies can provide an estimation of the frequency and nature of a side effect that is expected to occur in clinical practice. Findings from studies in animals may be relevant for humans and in the absence of data in humans suggest a potential safety concern that awaits clinical confirmation.
Risk factors and risk groups	Risk factors for neutropenia caused by cancer chemotherapies include increasing age, abnormal liver enzyme laboratory values, female gender, underweight, radiation therapy to the bone marrow, type of prior chemotherapy, and type of current treatment [Fontanella et al, 2014]. When SG is metabolised in the body, the active metabolite SN-38 is inactivated by an enzyme called uridine 5'-diphospho (UDP)-glucuronosyltransferase (UGT). Patients with reduced activity of this enzyme, such as patients who are homozygous for the *28 allele of UGT1A1, who are treated with SG may have an increased risk of neutropenia and accordingly, an increased risk of serious infection.
Risk Minimisation Measures	Routine risk minimisation measures: • Dose modifications based on severity and occurrence in SmPC section 4.2 • Warnings of severe or life-threatening neutropenia in SmPC section 4.4 • Warning for UGTA1A1*28 allele homozygous patients in SmPC section 4.4 • Adverse reaction in SmPC section 4.8 • Guidance for treating severe neutropenia relating to overdose in SmPC section 4.9 • Warning in PL section 2 • Side effect in PL section 4 • Restricted medical prescription Additional risk minimisation measures: • None

Important Identified Risk	**Severe diarrhoea**
Evidence for linking the risk to the medicine	Severe diarrhoea occurred in 10.7% of 366 patients treated with SG in the clinical studies. The dose of SG was interrupted in 2.7% patients and reduced in 2.2% patients, but no patients had to permanently discontinue treatment because of severe diarrhoea. Gastrointestinal disturbance was one of the main toxicities seen in animal studies. Clinical studies can provide an estimation of the frequency and nature of a side effect that is expected to occur in clinical practice. Findings from studies in animals may be relevant for humans and in the absence of data in humans suggest a potential safety concern that awaits clinical confirmation.
Risk factors and risk groups	Diarrhoea caused by SG may have similar risk factors as irinotecan because SN-38, once released from SG, is expected to be metabolised and excreted in the same way as SN-38 from irinotecan. The main clinical predictive factors for irinotecan-related diarrhoea are weekly administration, poor performance status, high levels of creatinine in blood, previous abdominopelvic radiotherapy, low leukocyte counts, age over 70 years, and two inherited conditions (Gilbert disease and Crigler-Najjar syndrome type 1) [Stein, 2010].
Risk Minimisation Measures	Routine risk minimisation measures: • Dose modifications based on severity and occurrence in SmPC section 4.2 • Warning of severe diarrhoea and recommendation for medication/supportive measures in SmPC section 4.4 • Adverse reaction in SmPC section 4.8 • Warning in PL section 2 • Side effect in PL section 4 • Restricted medical prescription Additional risk minimisation measures: • None
Important Identified Risk	**Hypersensitivity**
Evidence for linking the risk to the medicine	In the clinical studies 36.6% of 366 patients treated with SG developed hypersensitivity, and in 1.9% patients the hypersensitivity was severe. The dose of SG was interrupted in 0.8% patients and 0.3% patients had to permanently discontinue SG treatment. There were no dose reductions related to hypersensitivity. Animal studies showed that SG was well tolerated. Clinical studies can provide an estimation of the frequency and nature of a side effect that is expected to occur in clinical practice. Findings from studies in animals may be relevant for humans and in the absence of data in humans suggest a potential safety concern that awaits clinical confirmation.

Risk factors and risk groups	Risk factors for drug hypersensitivity reactions can be related to the medicine itself, to the characteristics of the individual patient receiving the medicine, and to other ongoing diseases. Medicine-related factors include metabolic products/cytotoxicity, high-dose and prolonged therapy, exposure to cross-reactive epitopes, repeated treatments with the same medicine, intravenous route of administration, and when multiple other medicines are used at the same time. Patient-related factors include a previous history with the same medicine or other similar medicines, multiple drug allergy syndrome, family history of hypersensitivity, female gender, and genetic factors. Illnesses such as infections (eg, HIV) and long-term diseases (eg, long-term kidney disease, heart diseases and malignancies) may also have an important influence on the development of allergic reactions to medicines by altering metabolic pathways and making changes to how the body's immune cells respond to medicines [Gomes 2017].
Risk Minimisation Measures	Routine risk minimisation measures: • Guidance for patient monitoring in SmPC section 4.2 and 4.4, respectively • Contraindication in SmPC section 4.3 and PL section 2 • Warning for severe hypersensitivity in SmPC section 4.4 • Adverse reaction in SmPC section 4.8 • Warning in PL section 2 • Side effect in PL section 4 • Restricted medical prescription Additional risk minimisation measures: • None
Important Potential Risk	**Embryo-foetal toxicity**
Evidence for linking the risk to the medicine	Use of SG during pregnancy has not been evaluated in the clinical studies and there are no data available for SG exposure in pregnant women. However, SG contains a component that is toxic to rapidly dividing cells. Based on its mechanism of action, SG can cause malformations or death in the unborn child when administered to a pregnant woman. Findings from studies in animals may be relevant for humans and in the absence of data in humans suggest a potential safety concern that awaits clinical confirmation.
Risk factors and risk groups	Women in their reproductive years and men with female partners in their reproductive years who are not using an effective method of contraception during treatment with SG and for 6 months and 3 months, respectively, after the last dose are at risk of toxicity to the unborn child.

Risk Minimisation Measures	Routine risk minimisation measures: • Warning and information of the risk of teratogenicity and/or embryo-foetal lethality in SmPC section 4.4 and 4.6, respectively • Warning and recommendation to verify the pregnancy status of women of childbearing potential prior to use in SmPC section 4.4 and 4.6, respectively • Recommendation in the case of pregnancy to immediately contact the doctor in SmPC section 4.6 • Recommendation for use of effective contraception during treatment and for up to 6 months after the last dose for female patients and up to 3 months after the last dose for male patients with female partners of childbearing potential in SmPC section 4.6 • Information that SN-38 was clastogenic in SmPC section 5.3 • Warning that TRODELVY should not be used during pregnancy in PL section 2 • Warning to use effective contraception in PL section 2 • Restricted medical prescription Additional risk minimisation measures: • None
Missing information	**Use in patients with moderate or severe hepatic impairment**
Risk Minimisation Measures	Routine risk minimisation measures: • Guidance that no dose adjustment is necessary for mild hepatic impairment in SmPC section 4.2 • Guidance that TRODELVY should be avoided in patients with moderate or severe hepatic impairment in SmPC section 4.2 • Information on SG exposure in patients with hepatic impairment in SmPC section 5.2 • Guidance for the patient to talk to their doctor or nurse if they have liver problems in PL section 2 • Restricted medical prescription Additional risk minimisation measures: • None
Additional Pharmacovigilance activities	Additional pharmacovigilance activities: • Study IMMU-132-15 See Section II.C of this summary for an overview of the post-authorisation development plan.
Missing information	**Immunogenicity**

Risk Minimisation Measures	Routine risk minimisation measures • Information that available data are limited, and no conclusion can be drawn on the impact of treatment-emergent ADAs on the efficacy and safety of SG in SmPC section 4.8 • Restricted medical prescription Additional risk minimisation measures: • None

II.C. Post-authorisation Development Plan

II.C.1. Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of TRODELVY.

II.C.2. Other Studies in Post-Authorisation Development Plan

Table Part VI.3. Other Studies in Post-Authorisation Development Plan

Short Study Name	Purpose of the Study
Study IMMU-132-15 A Phase 1, Open-Label, Dose-Escalation Study to Determine an Appropriate Starting Dose of Sacituzumab Govitecan in Subjects with Advanced or Metastatic Solid Tumour and Moderate Liver Impairment	The purpose of this study is: To identify the safe starting dose of TRODELVY in subjects with solid tumour and moderate hepatic impairment. To evaluate the pharmacokinetics of TRODELVY, free SN-38, total SN-38, and SN-38G in subjects with solid tumour and moderate hepatic impairment. To assess the occurrences of human antibodies against TRODELVY in subjects with solid tumour and moderate hepatic impairment.

List of references for the RMP Public Summary

Fontanella C, Bolzonello S, Lederer B, et al. Management of breast cancer patients with chemotherapy-induced neutropenia or febrile neutropenia. Breast Care. 2014;9:239-245.

Gomes ER, Kuyucu S. Epidemiology and risk factors in drug hypersensitivity reactions. Curr Treat Options Allergy. 2017;4:239-257.

Stein A, Voigt W, Jordan K. Chemotherapy-induced diarrhea: pathophysiology, frequency and guideline-based management. Ther Adv Med Oncol. 2010;2(1):51-63.